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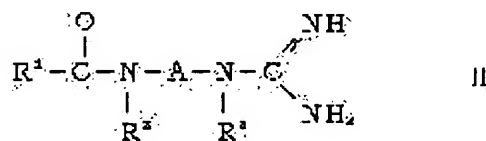
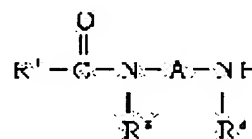
OOYAMA NOBUHIRO

(54) PRODUCTION OF GUANIDINE DERIVATIVE OR ITS SALT CONTAINING AMIDO GROUP

(57)Abstract:

PURPOSE: To obtain the subject derivative having high purity and excellent solubility, etc., by subjecting an amidoamine to a specific treatment, e.g. warming under reduced pressure and then, directly or after holding in an atmosphere free from carbon dioxide, to guanidination and removing impurities.

CONSTITUTION: The compound of formula II is obtained by subjecting an amidoamine of formula I (R¹ is 1-22C alkyl or alkenyl; R² and R³ are H or 1-4C alkylhydroxyalkyl; A is 1-10C alkylene or alkenylene) to a warming and pressure-reducing treatment or a warming and nitrogen-bubbling treatment (under the inner pressure reduced about 10-700hPa at 60-150°C for 10min to 3hr) and then, directly or after holding in an atmosphere free from carbon dioxide (e.g. in an atmosphere of inert gas such as nitrogen or helium at room temperature), to guanidination reaction in the presence of an alcohol and ether solvent and removing impurities by crystallization.



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CLAIMS

[Claim(s)]

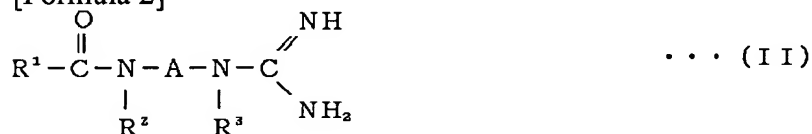
[Claim 1] The following general formula (I) (** 1)

[Formula 1]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. the amide amine expressed -- warming -- reduced pressure processing or warming -- the carbon dioxide immediately after carrying out nitrogen bubbling processing -- the following general formula (II) (** 2) characterized by guanidine-izing using a guanidine-ized reaction agent and subsequently removing an impurity after saving under a free ambient atmosphere

[Formula 2]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. The amide group content guanidine derivative expressed or the manufacture approach of the salt.

[Claim 2] The amide group content guanidine derivative according to claim 1 characterized by carrying out to the bottom of existence of little alcohols or ether in case the guanidine-ized reaction of said amide amine is performed, or the manufacture approach of the salt.

[Claim 3] The amide group content guanidine derivative according to claim 1 with which a means to remove said impurity is characterized by being crystallization, or the manufacture approach of the salt.

[Claim 4] The amide group content guanidine derivative according to claim 3 characterized by being beyond the temperature from which the solubility to the crystallization solvent of the bis-amide in which a crystal deposit and filtration temperature carry out a byproduction at a guanidine-ized reaction process becomes at least 0.1% in said crystallizing process, or the manufacture approach of the salt.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the manufacture approach of the high grade guanidine derivative containing the amide group for applying a guanidine derivative with strong base nature to a wide range application, or its salt.

[0002]

[Description of the Prior Art] The compound which has a guanidine radical has been used for fields, such as drugs, agricultural chemicals, a germicide, an insecticide, a useful metal scavenger, and a chelating agent, taking advantage of the strong base nature and antibacterial. However, it is only that the application as a surface active agent which employed the basicity efficiently has examples of a small number of, such as an arginine derivative and an amide group content guanidine derivative.

[0003] It is mentioned that it is sticky, or becomes a heavy result, and a difficulty is in the result engine performance although it excels in adsorbent [to the fiber or hair by the cationicity] when the compound of the structure where the 1st reason makes a straight chain alkyl group a lipophilic group, and makes a guanidine base a hydrophilic group is used as for example, the softening agent for fiber or a rinse agent for hair.

[0004] Generally the 2nd reason is because the purification method of a guanidine derivative is complicated. Conventionally, purification methods, such as preparative isolation liquid chromatography, a column chromatography, solvent extraction, and recrystallization, are combined and used after the reaction if needed.

[0005] An arginine derivative or an amide group content guanidine derivative is finished as indicated by JP,51-22055,B, JP,2-80667,A, JP,2-243614,A, and JP,4-34080,A, and even if the engine performance is good and compares with the general-purpose fourth class ammonium mold cationic surface active agent, it has the more excellent engine performance. However, the purification method is still complicated, and when what was refined by the above-mentioned purification method is used as water and/or an alcoholic solution, insoluble matter may produce it. For example, when these derivatives are used as a charge of hair makeup, a problem may arise at stability for mixture of the impurity of a minute amount.

[0006] Therefore, development of the rational manufacturing method of the amide group content guanidine derivative excellent in the solubility to the water and/or alcohol which a variation occurs according to structure among the arginine derivative of high performance and an amide group content guanidine derivative, and are considered that manufacture is more cheaply possible was desired.

[0007]

[Problem(s) to be Solved by the Invention] This invention aims at offering the approach of manufacturing advantageously the amide group content guanidine derivative which was moreover excellent in the solubility to water and/or alcohol, and stability with the high grade, or its salt.

[0008]

[Means for Solving the Problem] According to this invention, it is the following general formula (I) (**

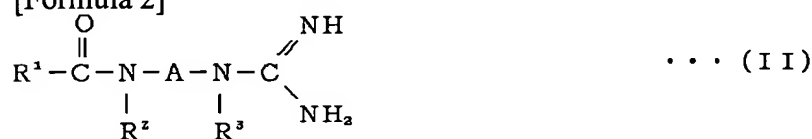
1).

[Formula 1]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. the amide amine expressed -- warming -- reduced pressure processing or warming -- the carbon dioxide immediately after carrying out nitrogen bubbling processing -- the following general formula (II) (** 2) characterized by guanidine-izing using a guanidine-ized reaction agent and subsequently removing an impurity after saving under a free ambient atmosphere

[Formula 2]



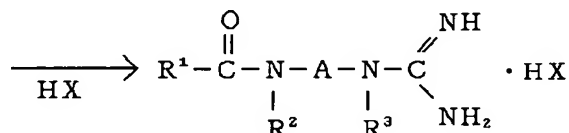
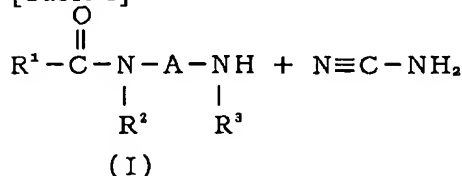
(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. The manufacture approach of the amide group content guanidine derivative expressed or its salt is offered. carrying out to the bottom of existence of little alcohols or ether, in case the guanidine-ized reaction of said amide amine is performed especially -- or In that a means to remove said impurity is crystallization, and this crystallizing process The manufacture approach of said amide group content guanidine derivative characterized by being beyond the temperature from which the solubility to the crystallization solvent of the bis-amide in which a crystal deposit and filtration temperature carry out a byproduction at a guanidine-ized reaction process especially becomes at least 0.1%, respectively, or its salt is offered.

[0009] Namely, the result to which this invention persons repeated research wholeheartedly in this present condition, an amide amine -- warming -- reduced pressure processing or warming -- immediately after carrying out nitrogen bubbling processing Or after saving under a carbon-dioxide free-lancer's ambient atmosphere (for example, under nitrogen-gas-atmosphere mind), It guanidine-izes by the usual approach, controlling reaction temperature, and the insoluble matter in water and/or an alcoholic solution is solved. Crystallization etc. by comparatively easy and one step of actuation A header and this invention were completed for the ability of the amide group content guanidine derivative which is a high grade and was excellent in the solubility to water and/or alcohol to be manufactured.

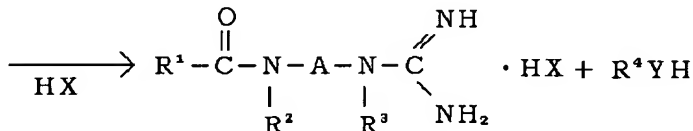
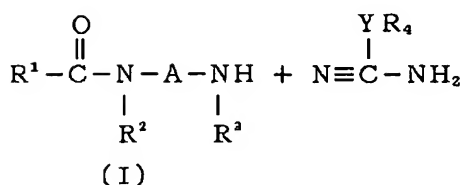
[0010] Hereafter, this invention is further explained to a detail. The reaction in the manufacture approach of this invention is shown by the reaction formula (I) of Table 1, (II), etc. below. This invention is ** amide amine (for example, with the diamine which has the first class and/or the second class amino group). it obtains at a reaction with a common acylating agent -- having -- pretreatment of said this invention -- carrying out -- subsequently -- **, controlling reaction temperature by the approach of adding solvents, such as little alcohols or ether, and controlling side reaction Under a general inorganic acid or organic-acid existence, a guanidine-ized reaction is performed by the usual reaction agents, such as a cyanamide and S-methyl iso thiourea. A small amount of unreacted amide amine which obtains an amide group content guanidine derivative rough reactant, and is contained in ** rough

reactant, By removing a bis-amide, a byproduction **** derivative, etc. of an unreacted guanidine-ized agent and the diamine which carries out a byproduction according to one step of purification process It is related with the approach of obtaining the high grade amide group content guanidine derivative excellent in stability, without producing sediment in the passage of time, when it is made water and/or an alcoholic solution.

[Table 1]



...反応式 (I)



...反応式 (II)

(R1, R2, R3, and A are the same radicals as the above among a formula.) R4 is the alkyl group of the straight chain of carbon numbers 1-4, or branched chain. HX expresses an inorganic acid or an organic acid. Y is S or O.

[0011] this invention -- using -- an amide amine is compoundable by the well-known approach. The diamine part of an amide amine is diamine which has the first class and/or the second class amino group, and can be expressed with the following general formula (III) (** 3).

[Formula 3]

R2-NH-A-NH-R3 ... (III)

(R2 and R3 are a hydrogen atom or the alkyl group of carbon numbers 1-4, and a hydroxyalkyl radical among a formula.) A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. As an example of diamine Diamino methane, ethylenediamine, N-methyl ethylene diamine, N and N'-dimethyl ethylenediamine, N-ethyl ethylenediamine, N and N'-diethyl ethylenediamine, N-propyl ethylenediamine, N and N'-dipropyl ethylenediamine, N-butyl ethylenediamine, N and N'-dibutyl ethylenediamine, N-tertiary butyl ethylenediamine, N, N'-JI tertiary butyl ethylenediamine and N-methyl-N' ethyl ethylenediamine, 1, 2-diaminopropane, a 1-methylamino-2-amino propane, A 1-amino-2-methylamino propane, 1, 3-diaminopropane, 3-methylamino propylamine, 1, 3-JI (methylamino) propylamine, 3-ethylamino propylamine, 3-propylamino propylamine, 3-butylamino propylamine, the 3-third butylamino propylamine, 3-(2-hydroxyethylamino)

propylamine, 1, 2-diamino butane, A 1,4-diaminobutane, 1, and 3-diamino-1-methyl propane, 1, 3-diamino-isobutane, 1, and 4-diamino-1-methyl butane, 1, 4-diamino-2-methyl butane, 1, 6-diaminohexan, 1, 8-diamino octane, 1, 10-diamino decane, etc. are raised. These can be used combining independent or two sorts or more.

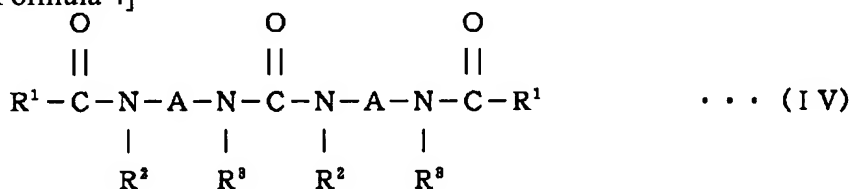
[0012] The acyl part of an amide amine is the short chain or long-chain-fatty-acid residue of a straight chain or branched chain, and an acetic acid, a propionic acid, butanoic acid, an isobutyric acid, a caproic acid, an octanoic acid, a capric acid, a lauric acid, a myristic acid, a palmitic acid, stearin acid, isostearic acid, oleic acid, an elaidic acid, linolic acid, a linolenic acid, arachidic acid, behenic acid, palm oil fatty acid, a palm-kernel-oil fatty acid, a palm oil fatty acid, a beef tallow fatty acid, etc. are raised. These can be used combining independent or two sorts or more.

[0013] As for the guanidine-ized reaction agent used for this invention, a cyanamide, S-methyl iso thiourea, S-ethyl iso thiourea, O-methylisourea, an O-ethyl iso urea, etc. are mentioned.

[0014] As described above, the amide group content guanidine in this invention approach or its salt pretreats an amide amine, subsequently is made to guanidine--ization-react, and is obtained by refining. Although pretreatment conditions, a reaction condition, and purification conditions are influenced by physical properties, such as a reaction agent, they take for an example the case where mono-lauroyl ethylenediamine (an amide amine and abbreviated name) is guanidine-ized by the cyanamide here, and show a reaction condition below.

[0015] first, ** amide amine -- warming -- reduced pressure processing or warming -- nitrogen bubbling processing or a carbon dioxide -- it saves under a free ambient atmosphere (for example, under nitrogen-gas-atmosphere mind). warming -- reduced pressure ****, when not carrying out a certain ***** nitrogen bubbling processing, or when it saves under the ambient atmosphere containing a carbon dioxide An amide amine absorbs a carbon dioxide and the byproduction of the urea derivative shown in the following general formula (IV) and (** 4) in process of the guanidine-ized reaction performed to a degree is carried out. the case where precipitate is produced in the passage of time when it considers as after [purification] water, and/or an alcoholic solvent -- it is -- warming -- reduced pressure processing and warming -- nitrogen bubbling processing or a carbon dioxide -- the preservation under a free ambient atmosphere (for example, under nitrogen-gas-atmosphere mind) is indispensable.

[Formula 4]



(R1, R2, R3, and A are the same radicals as the above among a formula.)

[0016] usually, warming -- reduced pressure processing or warming -- the temperature of about 60 degrees C - 150 degrees C to which an amide amine fuses nitrogen bubbling processing under reduced pressure of internal pressure extent of 10-700hPa (10 - 500mmHg) -- it is -- 10 minutes - 3 hours -- carrying out -- moreover, a carbon dioxide -- preservation under a free ambient atmosphere is performed in ordinary temperature just before reaction preparation under inert gas ambient atmospheres, such as nitrogen, helium, neon, and an argon.

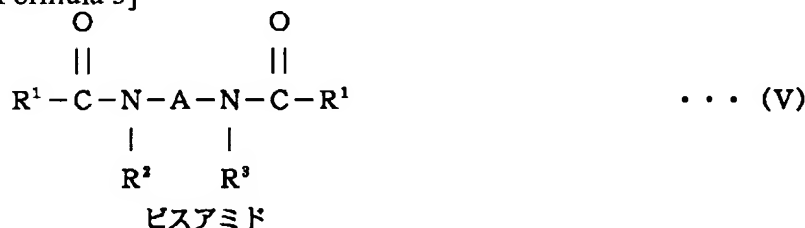
[0017] Subsequently, the amide amine of which ** pretreatment was done is neutralized by organic acids, such as inorganic acids, such as a hydrochloric acid, and an acetic acid, etc., and a cyanamide is warmed more than the melting point with fine particles, or it dissolves in ether system solvents, such as alcoholic solvent, such as more isopropyl alcohol than the amount of saturation solubility, or a tetrahydrofuran, and adds by a package or dropping. In cyanamide dropping, especially dropping time amount is not restricted, but the range of 0.1 - 3 hours after a viewpoint of manufacture effectiveness is desirable. The range of 60 degrees C - 120 degrees C of reaction temperature is 80 degrees C - 100

degrees C preferably. It is unsuitable, also when a reaction rate is slow, side reaction which is not desirable, such as a polymerization reaction of a cyanamide, occurs above 120 degrees C and it is any below 60 degrees C. In addition, if a cyanamide is added with a non-solvent, reaction temperature control will take cautions for exothermic reaction, but when it reacts to the bottom of existence of alcohols or ether, reaction temperature control is easy and desirable.

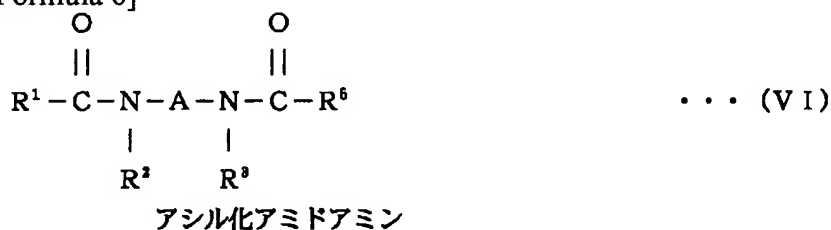
[0018] ** Refine the amide group content guanidine derivative rough reactant obtained in this way by the purification approach described below. If it is refined by the usual purification approach, an amide group content guanidine derivative rough reactant is satisfactory, when an impurity can remove considerably and uses it with fine particles, but since existence of a little impurity has big effect at the preservation stability of a product on it when producing commercially for the application of cosmetics, drugs, and others after pharmaceutical preparation-izing of a water solution, an emulsification object, etc., it is necessary to remove these impurities even in a minute amount.

[0019] Impurities are an unreacted raw material compound and a by-product. Although it can predict easily that an unreacted amide amine, an unreacted cyanamide, and a dicyandiamide are contained to an impurity, these three sorts of compounds are fully removed, and when what was made into the content 0 as a matter of fact is used as water and/or an alcoholic solution, precipitate of a minute amount may produce it. When this invention persons collected these precipitate and dissociated and analyzed, they found out that it was the cause of precipitate of the compound expressed with the following general formula (V) and (VI). Since the solubility to water and/or alcohol is low, each of these is precipitating and deposits.

[Formula 5]



[Formula 6]



$$\begin{array}{c}
 \text{O} \\
 || \\
 \text{R}^5 - \text{C} - \text{OH}
 \end{array}$$
 (グアニジン化の際、酸として、有機酸R⁵-C-OHを用いた場合生成する。

[0020] Although impurity removal of a bis-amide etc. can adopt many approaches, it is above desirable to carry out on condition that the following for example, when crystallization refines. After solubility of a guanidine derivative like a tetrahydrofuran and a methyl ethyl ketone carries out addition of the solvent which changes with temperature a lot two to 10 times (weight ratio), warms it to an amide group content guanidine derivative rough reactant till the boiling point and filters it as occasion demands to it at the time of heat, it cools gradually. Although the solubility to crystallization solvents, such as a bis-amide shown in said general formula (V) and (VI), is temperature-dependent and solubility changes rapidly bordering on a certain temperature It maintains at the constant temperature beyond the

temperature from which the solubility of the lower compound of the inner solubility of the bis-amide shown especially in a general formula (V) and (VI) becomes at least 0.1%, after crystallizing the specified substance enough, it filters, and the vacuum drying of the crystal is carried out, and a solvent is removed. There is a fault of ** -- the amount of solvents to apply cannot serve as hyperviscosity during crystallization actuation by under 2 double, or cannot remove an impurity enough -- when [than 10 times] more, yield is low, and it is not desirable also when it is any. Moreover, when the solubility to the crystallization solvent of a compound with the lower solubility in the inner crystallization temperature of the bis-amide shown in a general formula (V) and (VI) is the temperature which is less than 0.1% and a refined material is used as water and/or an alcoholic solution, precipitate of a minute amount may be accepted by the passage of time, and it is not desirable.

[0021] By the above actuation, the amide group content guanidine which is a high grade and was excellent in the solubility to water and/or alcohol and the stability in a solution condition, or its salt can be manufactured.

[0022]

[Example] Although an example is given below and being further explained to a detail, this invention is not limited to these. In addition, % is weight criteria.

[0023] Example 1 It decompresses, teaching mono-lauroyl ethylenediamine (97.2% unreacted lauric acid: purity : abbreviation, 0.8%, bis-amide : 2.0%) 121g (0.5 mols) to 500ml 4 Thu opening flask equipped with the pretreatment agitator of the synthetic (1) mono-lauroyl ethylenediamine of a lauroyl amide ethyl guanidine hydrochloride, a thermometer, and a vacuum and nitrogen installation tubing, and keeping at 80 degrees C. Nitrogen installation was repeated 3 times and carried out the nitrogen purge.

[an amide amine, and]

[0024] (2) It dropped and neutralized to the amide amine in which the lauroyl amide ethyl guanidine hydrochloride carried out synthetic pretreatment, being careful of 48.2g (36%) (0.475 mols) of concentrated hydrochloric acid for whenever [system internal temperature] not to exceed 100 degrees C. another -- cyanamide 31.5g (0.75 mols) -- isopropyl alcohol 31.5g -- dissolving -- amide amine 95% - - it was dropped over 1 hour into the hydrochloride, keeping whenever [system internal temperature] at 80-90 degrees C. Aging was performed at the same temperature after dropping termination for 3 hours, and after adding and carrying out full neutralization of the 2.5g (36%) (0.025 mols) of the concentrated hydrochloric acid, reduced pressure distilling off of the solvent was carried out. yield: -- 170g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.5% from an amide amine, and purity: -- unreacted 88.1% -- amide amine:2.6% and byproduction dicyandiamide:7.0% -- bis--- it was byproduction urea derivative:trace amide:1.4%.

[0025] (3) 100g of rough products obtained by (2) was taken, tetrahydrofuran 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and the thermometer. At 1-degree-C a rate for /, it cooled to 40 degrees C over 40 minutes, after the crystal deposited, it was kept warm at 40 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, carried out the vacuum drying for 40-degree-C 2 hours, and the purification lauroyl amide ethyl guanidine hydrochloride was obtained. yield: -- 75g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.5%, less than [byproduction dicyandiamide:0.01%], and bis-amide: -- byproduction urea derivative:detection was not carried out 0.01% or less, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.5% at 40 degrees C.

[0026] Example 2 It decompresses, teaching mono-lauroyl butylene diamine (98.4% unreacted lauric acid: purity : abbreviation, 1.0%, bis-amide : 0.6%) 135g (0.5 mols) to 500ml 4 Thu opening flask equipped with the pretreatment agitator of the synthetic (1) mono-lauroyl butylene diamine of a lauroyl

amide butyl guanidine-acetic acid salt, a thermometer, and a vacuum and nitrogen installation tubing, and keeping at 80 degrees C. Nitrogen installation was repeated 3 times and carried out the nitrogen purge. [an amide amine, and]

[0027]

(2) It dropped and neutralized to the amide amine in which the lauroyl amide butyl guanidine-acetic acid salt carried out synthetic pretreatment, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- it was byproduction urea derivative:trace amide:0.4% and acetylation amide amine:1.6%.

[0028]

(3) 100g of rough products obtained by (2) was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 80g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.4% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.1%, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transperence solution for 25-degree-C six months. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.1% at 50 degrees C.

[0029] It dropped and neutralized to the mono-lauroyl ethylenediamine pretreated like the synthetic example 1 of an example 3(1) lauroyl amide ethyl guanidine-acetic acid salt (1), being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, the addition dissolution of the cyanamide 25.2g (0.6 mols) was carried out, and it reacted for 5 hours, sometimes cooling reaction temperature so that 90 degrees C may not be exceeded. yield: -- 176g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.2% from an amide amine, and purity: -- unreacted 91.1% -- amide amine:2.7% and byproduction dicyandiamide:3.1% -- bis--- it was byproduction urea derivative:trace amide:1.4% and acetylation amide amine:1.5%.

[0030]

(2) 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide ethyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine-acetic acid salts were obtained. yield: -- 79g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.4% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.01% or less, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transperence

solution for 25-degree-C six months. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0031] The tetrahydrofuran was used instead of isopropyl alcohol as a cyanamide dissolution solvent, and also it was made to react similarly in composition of the synthetic example 2(2) lauroyl amide butyl guanidine-acetic acid salt of an example 4(1) lauroyl amide butyl guanidine-acetic acid salt. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- it was byproduction urea derivative:trace amide:0.4% and acetylation amide amine:1.6%.

[0032]

(2) 100g of rough products obtained by (1) was taken, tetrahydrofuran 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 25 degrees C over 55 minutes, after the crystal deposited, it was kept warm at 25 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine-acetic acid salts were obtained. yield: -- 85g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.4% -- amide amine:0.5% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.1%, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.1% at 25 degrees C.

[0033] In pretreatment of example of comparison 1 example 2(1) mono-lauroyl butylene diamine Reduced pressure after leaving an amide amine for three days in ordinary temperature in atmospheric air A reaction and when crystallization is carried out, without performing a nitrogen purge by yield:82g, the liquid chromatograph, and thin layer chromatographic analysis purity: -- unreacted 98.5% -- amide amine:0.7% and less than [byproduction dicyandiamide:0.01%] -- bis--- they were less than [amide:0.05%], acetylation amide amine:0.4%, and byproduction urea derivative:0.3%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, precipitate was produced two days after 25 degree C.

[0034]

[Effect of the Invention] Moreover the amide group content guanidine derivative obtained by said manufacture approach of this invention and its salt are excellent in the stability in the soluble solution condition of water and/or alcohol at the high grade, and, moreover, can manufacture the amide group content guanidine derivative of the specified substance, or its salt advantageously industrially by the manufacture approach of this invention.

[Translation done.]

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TECHNICAL FIELD

[Industrial Application] This invention relates to the manufacture approach of the high grade guanidine derivative containing the amide group for applying a guanidine derivative with strong base nature to a wide range application, or its salt.

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PRIOR ART

[Description of the Prior Art] The compound which has a guanidine radical has been used for fields, such as drugs, agricultural chemicals, a germicide, an insecticide, a useful metal scavenger, and a chelating agent, taking advantage of the strong base nature and antibacterial. However, it is only that the application as a surface active agent which employed the basicity efficiently has examples of a small number of, such as an arginine derivative and an amide group content guanidine derivative.

[0003] It is mentioned that it is sticky, or becomes a heavy result, and a difficulty is in the result engine performance although it excels in adsorbent [to the fiber or hair by the cationicity] when the compound of the structure where the 1st reason makes a straight chain alkyl group a lipophilic group, and makes a guanidine base a hydrophilic group is used as for example, the softening agent for fiber or a rinse agent for hair.

[0004] Generally the 2nd reason is because the purification method of a guanidine derivative is complicated. Conventionally, purification methods, such as preparative isolation liquid chromatography, a column chromatography, solvent extraction, and recrystallization, are combined and used after the reaction if needed.

[0005] An arginine derivative or an amide group content guanidine derivative is finished as indicated by JP,51-22055,B, JP,2-80667,A, JP,2-243614,A, and JP,4-34080,A, and even if the engine performance is good and compares with the general-purpose fourth class ammonium mold cationic surface active agent, it has the more excellent engine performance. However, the purification method is still complicated, and when what was refined by the above-mentioned purification method is used as water and/or an alcoholic solution, insoluble matter may produce it. For example, when these derivatives are used as a charge of hair makeup, a problem may arise at stability for mixture of the impurity of a minute amount.

[0006] Therefore, development of the rational manufacturing method of the amide group content guanidine derivative excellent in the solubility to the water and/or alcohol which a variation occurs according to structure among the arginine derivative of high performance and an amide group content guanidine derivative, and are considered that manufacture is more cheaply possible was desired.

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EFFECT OF THE INVENTION

[Effect of the Invention] Moreover the amide group content guanidine derivative obtained by said manufacture approach of this invention and its salt are excellent in the stability in the soluble solution condition of water and/or alcohol at the high grade, and, moreover, can manufacture the amide group content guanidine derivative of the specified substance, or its salt advantageously industrially by the manufacture approach of this invention.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention aims at offering the approach of manufacturing advantageously the amide group content guanidine derivative which was moreover excellent in the solubility to water and/or alcohol, and stability with the high grade, or its salt.
[0008]

[Translation done.]

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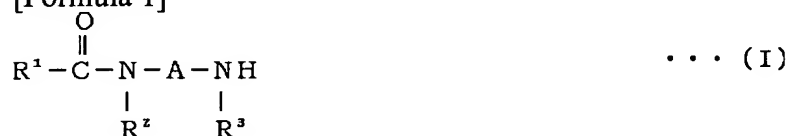
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MEANS

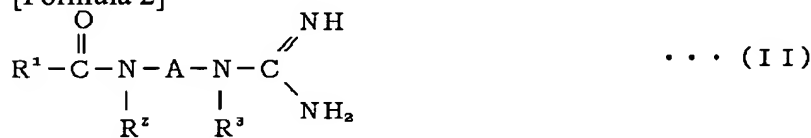
[Means for Solving the Problem] According to this invention, it is the following general formula (I) (** 1).

[Formula 1]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. the amide amine expressed -- warming -- reduced pressure processing or warming -- the carbon dioxide immediately after carrying out nitrogen bubbling processing -- the following general formula (II) (** 2) characterized by guanidine-izing using a guanidine-ized reaction agent and subsequently removing an impurity after saving under a free ambient atmosphere

[Formula 2]



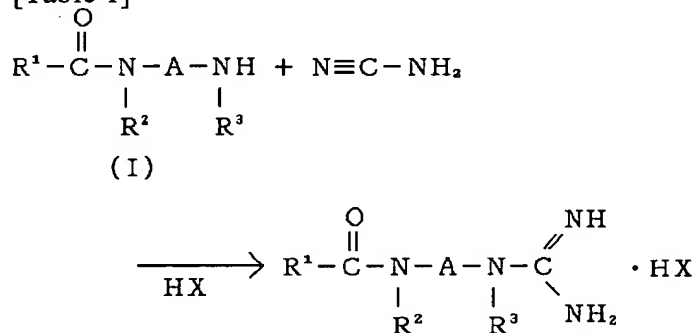
(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. The manufacture approach of the amide group content guanidine derivative expressed or its salt is offered. carrying out to the bottom of existence of little alcohols or ether, in case the guanidine-ized reaction of said amide amine is performed especially -- or In that a means to remove said impurity is crystallization, and this crystallizing process The manufacture approach of said amide group content guanidine derivative characterized by being beyond the temperature from which the solubility to the crystallization solvent of the bis-amide in which a crystal deposit and filtration temperature carry out a byproduction at a guanidine-ized reaction process especially becomes at least 0.1%, respectively, or its salt is offered.

[0009] Namely, the result to which this invention persons repeated research wholeheartedly in this present condition, an amide amine -- warming -- reduced pressure processing or warming -- immediately after carrying out nitrogen bubbling processing Or after saving under a carbon-dioxide free-lancer's ambient atmosphere (for example, under nitrogen-gas-atmosphere mind), It guanidine-izes by the usual

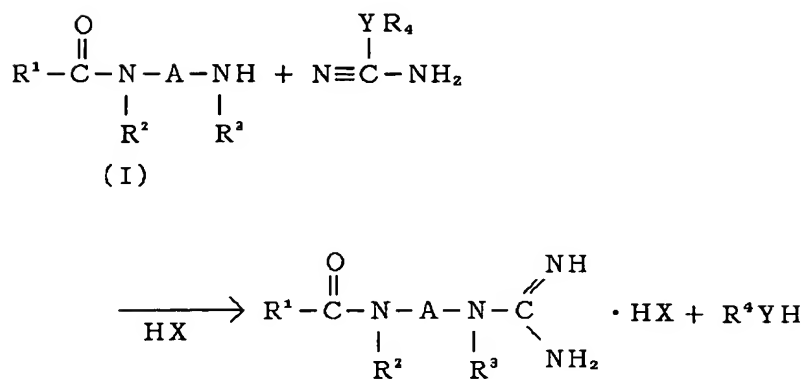
approach, controlling reaction temperature, and the insoluble matter in water and/or an alcoholic solution is solved. Crystallization etc. by comparatively easy and one step of actuation A header and this invention were completed for the ability of the amide group content guanidine derivative which is a high grade and was excellent in the solubility to water and/or alcohol to be manufactured.

[0010] Hereafter, this invention is further explained to a detail. The reaction in the manufacture approach of this invention is shown by the reaction formula (I) of Table 1, (II), etc. below. This invention is ** amide amine (for example, with the diamine which has the first class and/or the second class amino group). it obtains at a reaction with a common acylating agent -- having -- pretreatment of said this invention -- carrying out -- subsequently -- **, controlling reaction temperature by the approach of adding solvents, such as little alcohols or ether, and controlling side reaction Under a general inorganic acid or organic-acid existence, a guanidine-ized reaction is performed by the usual reaction agents, such as a cyanamide and S-methyl iso thiourea. A small amount of unreacted amide amine which obtains an amide group content guanidine derivative rough reactant, and is contained in ** rough reactant, By removing a bis-amide, a byproduction **** derivative, etc. of an unreacted guanidine-ized agent and the diamine which carries out a byproduction according to one step of purification process It is related with the approach of obtaining the high grade amide group content guanidine derivative excellent in stability, without producing sediment in the passage of time, when it is made water and/or an alcoholic solution.

[Table 1]



…反応式 (I)



…反応式 (II)

(R1, R2, R3, and A are the same radicals as the above among a formula.) R4 is the alkyl group of the straight chain of carbon numbers 1-4, or branched chain. HX expresses an inorganic acid or an organic acid. Y is S or O.

[0011] this invention -- using -- an amide amine is compoundable by the well-known approach. The diamine part of an amide amine is diamine which has the first class and/or the second class amino group,

and can be expressed with the following general formula (III) (** 3).

[Formula 3]

$R_2-NH-A-NH-R_3 \dots$ (III)

(R_2 and R_3 are a hydrogen atom or the alkyl group of carbon numbers 1-4, and a hydroxyalkyl radical among a formula.) A is the alkylene group or alkenylene group of the straight chain of carbon numbers 1-10, or branched chain. As an example of diamine Diamino methane, ethylenediamine, N-methyl ethylene diamine, N and N'-dimethyl ethylenediamine, N-ethyl ethylenediamine, N and N'-diethyl ethylenediamine, N-propyl ethylenediamine, N and N'-dipropyl ethylenediamine, N-butyl ethylenediamine, N and N'-dibutyl ethylenediamine, N-tertiary butyl ethylenediamine, N, N'-JI tertiary butyl ethylenediamine and N-methyl-N' ethyl ethylenediamine, 1, 2-diaminopropane, a 1-methylamino-2-amino propane, A 1-amino-2-methylamino propane, 1, 3-diaminopropane, 3-methylamino propylamine, 1, 3-JI (methylamino) propylamine, 3-ethylamino propylamine, 3-propylamino propylamine, 3-butylamino propylamine, the 3-third butylamino propylamine, 3-(2-hydroxyethylamino) propylamine, 1, 2-diamino butane, A 1,4-diaminobutane, 1, and 3-diamino-1-methyl propane, 1, 3-diamino-isobutane, 1, and 4-diamino-1-methyl butane, 1, 4-diamino-2-methyl butane, 1, 6-diaminohexan, 1, 8-diamino octane, 1, 10-diamino decane, etc. are raised. These can be used combining independent or two sorts or more.

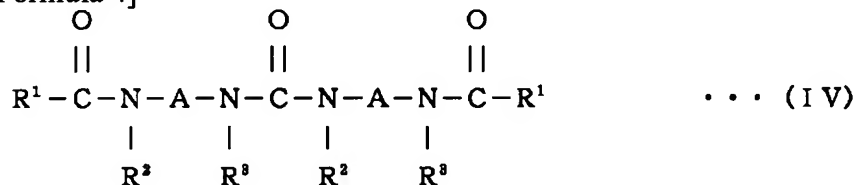
[0012] The acyl part of an amide amine is the short chain or long-chain-fatty-acid residue of a straight chain or branched chain, and an acetic acid, a propionic acid, butanoic acid, an isobutyric acid, a caproic acid, an octanoic acid, a capric acid, a lauric acid, a myristic acid, a palmitic acid, stearin acid, isostearic acid, oleic acid, an elaidic acid, linolic acid, a linolenic acid, arachidic acid, behenic acid, palm oil fatty acid, a palm-kernel-oil fatty acid, a palm oil fatty acid, a beef tallow fatty acid, etc. are raised. These can be used combining independent or two sorts or more.

[0013] As for the guanidine-ized reaction agent used for this invention, a cyanamide, S-methyl iso thiourea, S-ethyl iso thiourea, O-methylisourea, an O-ethyl iso urea, etc. are mentioned.

[0014] As described above, the amide group content guanidine in this invention approach or its salt pretreats an amide amine, subsequently is made to guanidine-ization-react, and is obtained by refining. Although pretreatment conditions, a reaction condition, and purification conditions are influenced by physical properties, such as a reaction agent, they take for an example the case where mono-lauroyl ethylenediamine (an amide amine and abbreviated name) is guanidine-ized by the cyanamide here, and show a reaction condition below.

[0015] first, ** amide amine -- warming -- reduced pressure processing or warming -- nitrogen bubbling processing or a carbon dioxide -- it saves under a free ambient atmosphere (for example, under nitrogen-gas-atmosphere mind). warming -- reduced pressure ****, when not carrying out a certain ***** nitrogen bubbling processing, or when it saves under the ambient atmosphere containing a carbon dioxide An amide amine absorbs a carbon dioxide and the byproduction of the urea derivative shown in the following general formula (IV) and (** 4) in process of the guanidine-ized reaction performed to a degree is carried out. the case where precipitate is produced in the passage of time when it considers as after [purification] water, and/or an alcoholic solvent -- it is -- warming -- reduced pressure processing and warming -- nitrogen bubbling processing or a carbon dioxide -- the preservation under a free ambient atmosphere (for example, under nitrogen-gas-atmosphere mind) is indispensable.

[Formula 4]



(R_1 , R_2 , R_3 , and A are the same radicals as the above among a formula.)

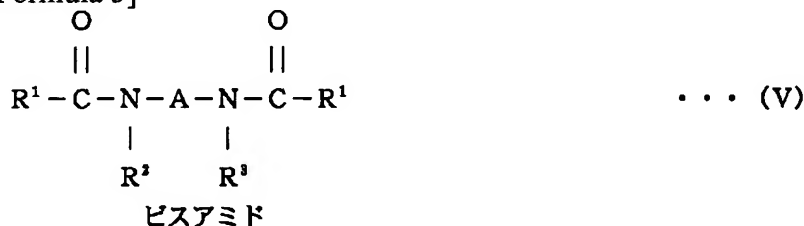
[0016] usually, warming -- reduced pressure processing or warming -- the temperature of about 60 degrees C - 150 degrees C to which an amide amine fuses nitrogen bubbling processing under reduced pressure of internal pressure extent of 10-700hPa (10 - 500mmHg) -- it is -- 10 minutes - 3 hours -- carrying out -- moreover, a carbon dioxide -- preservation under a free ambient atmosphere is performed in ordinary temperature just before reaction preparation under inert gas ambient atmospheres, such as nitrogen, helium, neon, and an argon.

[0017] Subsequently, the amide amine of which ** pretreatment was done is neutralized by organic acids, such as inorganic acids, such as a hydrochloric acid, and an acetic acid, etc., and a cyanamide is warmed more than the melting point with fine particles, or it dissolves in ether system solvents, such as alcoholic solvent, such as more isopropyl alcohol than the amount of saturation solubility, or a tetrahydrofuran, and adds by a package or dropping. In cyanamide dropping, especially dropping time amount is not restricted, but the range of 0.1 - 3 hours after a viewpoint of manufacture effectiveness is desirable. The range of 60 degrees C - 120 degrees C of reaction temperature is 80 degrees C - 100 degrees C preferably. It is unsuitable, also when a reaction rate is slow, side reaction which is not desirable, such as a polymerization reaction of a cyanamide, occurs above 120 degrees C and it is any below 60 degrees C. In addition, if a cyanamide is added with a non-solvent, reaction temperature control will take cautions for exothermic reaction, but when it reacts to the bottom of existence of alcohols or ether, reaction temperature control is easy and desirable.

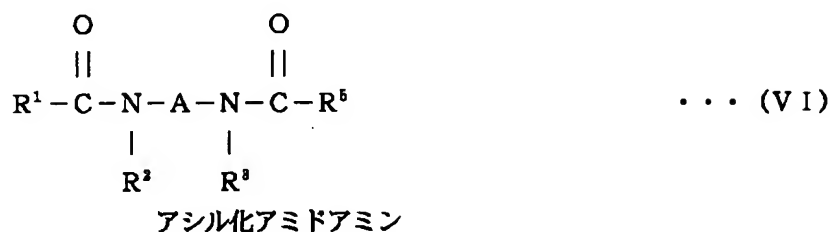
[0018] ** Refine the amide group content guanidine derivative rough reactant obtained in this way by the purification approach described below. If it is refined by the usual purification approach, an amide group content guanidine derivative rough reactant is satisfactory, when an impurity can remove considerably and uses it with fine particles, but since existence of a little impurity has big effect at the preservation stability of a product on it when producing commercially for the application of cosmetics, drugs, and others after pharmaceutical preparation-izing of a water solution, an emulsification object, etc., it is necessary to remove these impurities even in a minute amount.

[0019] Impurities are an unreacted raw material compound and a by-product. Although it can predict easily that an unreacted amide amine, an unreacted cyanamide, and a dicyandiamide are contained to an impurity, these three sorts of compounds are fully removed, and when what was made into the content 0 as a matter of fact is used as water and/or an alcoholic solution, precipitate of a minute amount may produce it. When this invention persons collected these precipitate and dissociated and analyzed, they found out that it was the cause of precipitate of the compound expressed with the following general formula (V) and (VI). Since the solubility to water and/or alcohol is low, each of these is precipitating and deposits.

[Formula 5]



[Formula 6]



$$\begin{array}{c}
 \text{O} \\
 || \\
 \text{R}^5 - \text{C} - \text{OH}
 \end{array}$$

(グアニジン化の際、酸として、有機酸 $\text{R}^5 - \text{C} - \text{OH}$ を用いた場合生成する。)

[0020] Although impurity removal of a bis-amide etc. can adopt many approaches, it is above desirable to carry out on condition that the following for example, when crystallization refines. After solubility of a guanidine derivative like a tetrahydrofuran and a methyl ethyl ketone carries out addition of the solvent which changes with temperature a lot two to 10 times (weight ratio), warms it to an amide group content guanidine derivative rough reactant till the boiling point and filters it as occasion demands to it at the time of heat, it cools gradually. Although the solubility to crystallization solvents, such as a bis-amide shown in said general formula (V) and (VI), is temperature-dependent and solubility changes rapidly bordering on a certain temperature It maintains at the constant temperature beyond the temperature from which the solubility of the lower compound of the inner solubility of the bis-amide shown especially in a general formula (V) and (VI) becomes at least 0.1%, after crystallizing the specified substance enough, it filters, and the vacuum drying of the crystal is carried out, and a solvent is removed. There is a fault of ** -- the amount of solvents to apply cannot serve as hyperviscosity during crystallization actuation by under 2 double, or cannot remove an impurity enough -- when [than 10 times] more, yield is low, and it is not desirable also when it is any. Moreover, when the solubility to the crystallization solvent of a compound with the lower solubility in the inner crystallization temperature of the bis-amide shown in a general formula (V) and (VI) is the temperature which is less than 0.1% and a refined material is used as water and/or an alcoholic solution, precipitate of a minute amount may be accepted by the passage of time, and it is not desirable.

[0021] By the above actuation, the amide group content guanidine which is a high grade and was excellent in the solubility to water and/or alcohol and the stability in a solution condition, or its salt can be manufactured.

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EXAMPLE

[Example] Although an example is given below and being further explained to a detail, this invention is not limited to these. In addition, % is weight criteria.

[0023] Example 1 It decompresses, teaching mono-lauroyl ethylenediamine (97.2% unreacted lauric acid: purity : abbreviation, 0.8%, bis-amide : 2.0%) 121g (0.5 mols) to 500ml 4 Thu opening flask equipped with the pretreatment agitator of the synthetic (1) mono-lauroyl ethylenediamine of a lauroyl amide ethyl guanidine hydrochloride, a thermometer, and a vacuum and nitrogen installation tubing, and keeping at 80 degrees C. Nitrogen installation was repeated 3 times and carried out the nitrogen purge. [an amide amine, and]

[0024] (2) It dropped and neutralized to the amide amine in which the lauroyl amide ethyl guanidine hydrochloride carried out synthetic pretreatment, being careful of 48.2g (36%) (0.475 mols) of concentrated hydrochloric acid for whenever [system internal temperature] not to exceed 100 degrees C. another -- cyanamide 31.5g (0.75 mols) -- isopropyl alcohol 31.5g -- dissolving -- amide amine 95% - - it was dropped over 1 hour into the hydrochloride, keeping whenever [system internal temperature] at 80-90 degrees C. Aging was performed at the same temperature after dropping termination for 3 hours, and after adding and carrying out full neutralization of the 2.5g (36%) (0.025 mols) of the concentrated hydrochloric acid, reduced pressure distilling off of the solvent was carried out. yield: -- 170g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.5% from an amide amine, and purity: -- unreacted 88.1% -- amide amine:2.6% and byproduction dicyandiamide:7.0% -- bis--- it was byproduction urea derivative:trace amide:1.4%.

[0025] (3) 100g of rough products obtained by (2) was taken, tetrahydrofuran 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and the thermometer. At 1-degree-C a rate for /, it cooled to 40 degrees C over 40 minutes, after the crystal deposited, it was kept warm at 40 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, carried out the vacuum drying for 40-degree-C 2 hours, and the purification lauroyl amide ethyl guanidine hydrochloride was obtained. yield: -- 75g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.5%, less than [byproduction dicyandiamide:0.01%], and bis-amide: -- byproduction urea derivative:detection was not carried out 0.01% or less, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.5% at 40 degrees C.

[0026] Example 2 It decompresses, teaching mono-lauroyl butylene diamine (98.4% unreacted lauric acid: purity : abbreviation, 1.0%, bis-amide : 0.6%) 135g (0.5 mols) to 500ml 4 Thu opening flask equipped with the pretreatment agitator of the synthetic (1) mono-lauroyl butylene diamine of a lauroyl amide butyl guanidine-acetic acid salt, a thermometer, and a vacuum and nitrogen installation tubing, and keeping at 80 degrees C. Nitrogen installation was repeated 3 times and carried out the nitrogen

purge. [an amide amine, and]
[0027]

(2) It dropped and neutralized to the amide amine in which the lauroyl amide butyl guanidine-acetic acid salt carried out synthetic pretreatment, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- it was byproduction urea derivative:trace amide:0.4% and acetylation amide amine:1.6%.

[0028]

(3) 100g of rough products obtained by (2) was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 80g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.4% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.1%, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.1% at 50 degrees C.

[0029] It dropped and neutralized to the mono-lauroyl ethylenediamine pretreated like the synthetic example 1 of an example 3(1) lauroyl amide ethyl guanidine-acetic acid salt (1), being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, the addition dissolution of the cyanamide 25.2g (0.6 mols) was carried out, and it reacted for 5 hours, sometimes cooling reaction temperature so that 90 degrees C may not be exceeded. yield: -- 176g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.2% from an amide amine, and purity: -- unreacted 91.1% -- amide amine:2.7% and byproduction dicyandiamide:3.1% -- bis--- it was byproduction urea derivative:trace amide:1.4% and acetylation amide amine:1.5%.

[0030]

(2) 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide ethyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine-acetic acid salts were obtained. yield: -- 79g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.4% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.01% or less, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0031] The tetrahydrofuran was used instead of isopropyl alcohol as a cyanamide dissolution solvent, and also it was made to react similarly in composition of the synthetic example 2(2) lauroyl amide butyl guanidine-acetic acid salt of an example 4(1) lauroyl amide butyl guanidine-acetic acid salt. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- it was byproduction urea derivative:trace amide:0.4% and acetylation amide amine:1.6%.

[0032]

(2) 100g of rough products obtained by (1) was taken, tetrahydrofuran 300g was added, it heated at 80 degrees C, and the rough product was completely dissolved in 1l. 4 Thu opening flask equipped with the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and the thermometer. At 1-degree-C a rate for /, it cooled to 25 degrees C over 55 minutes, after the crystal deposited, it was kept warm at 25 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine-acetic acid salts were obtained. yield: -- 85g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.4% -- amide amine:0.5% and less than [byproduction dicyandiamide:0.01%] -- bis--- less than [amide:0.01%] and acetylation amide amine: - byproduction urea derivative:detection was not carried out 0.1%, but it came out. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was a transparence solution for 25-degree-C six months. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.1% at 25 degrees C.

[0033] In pretreatment of example of comparison 1 example 2(1) mono-lauroyl butylene diamine Reduced pressure after leaving an amide amine for three days in ordinary temperature in atmospheric air A reaction and when crystallization is carried out, without performing a nitrogen purge by yield:82g, the liquid chromatograph, and thin layer chromatographic analysis purity: -- unreacted 98.5% -- amide amine:0.7% and less than [byproduction dicyandiamide:0.01%] -- bis--- they were less than [amide:0.05%], acetylation amide amine:0.4%, and byproduction urea derivative:0.3%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, precipitate was produced two days after 25 degree C.

[Translation done.]

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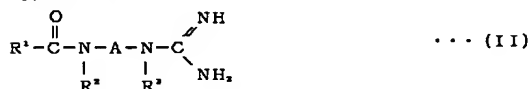
(54)【発明の名称】 アミド基含有グアニジン誘導体またはその塩の製造方法

(57)【要約】

【目的】 高純度でかつ水および／またはアルコールへの溶解性、溶液状態での安定性に優れたアミド基含有グアニジン誘導体またはその塩の製造方法を提供する。

【構成】 アミドアミンを、加温減圧処理、加温窒素バブリング処理直後、もしくは二酸化炭素フリーの雰囲気下で保存後、シアナミド、S-メチルイソチオ尿素等の通常のグアニジン化反応試剤でグアニジン化し、さらに混在する不純物を晶析等の手段により除去することを特徴とする下記一般式(II)で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法。

【化2】



(式中、R¹は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R²、R³は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシアルキル基であり、同一でも異なっても良い。Aは、炭素数1～10の直鎖ま

たは分岐鎖のアルキレン基あるいはアルケニレン基である。)

1

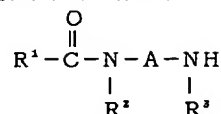
2

【特許請求の範囲】

*【化1】

【請求項1】 下記一般式(I)(化1)

*

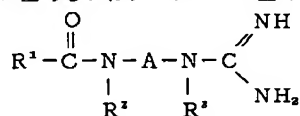


... (I)

(式中、R¹は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R²、R³は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっても良い。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基であ

※る。)で表わされるアミドアミンを、加温減圧処理あるいは加温窒素バブリング処理をした直後、もしくは二酸化炭素フリーの雰囲気下で保存した後、グアニジン化反応試剤を用いてグアニジン化し、次いで不純物を除去することを特徴とする下記一般式(II)(化2)

【化2】



... (II)

(式中、R¹は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R²、R³は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっても良い。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基である。)で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項2】 前記アミドアミンのグアニジン化反応を行なう際に、少量のアルコール類またはエーテル類の存在下に行なうことを特徴とする請求項1記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項3】 前記不純物を除去する手段が、晶析であることを特徴とする請求項1記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項4】 前記晶析工程において、結晶析出および濾過温度が、グアニジン化反応工程で副生するビスアミドの晶析溶媒に対する溶解度が、少なくとも0.1%となる温度以上であることを特徴とする請求項3に記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、強塩基性を持つグアニジン誘導体を広範囲の用途に適用するための、アミド基を含有する高純度グアニジン誘導体またはその塩の製造方法に関する。

【0002】

【従来の技術】グアニジン基を有する化合物は、その強塩基性、抗菌性を生かし、医薬品、農薬、殺菌剤、殺虫剤、有用金属捕集剤、キレート剤等の分野に使用されてきた。しかし、その塩基性を生かした、界面活性剤としての応用例は、アルギニン誘導体、アミド基含有グアニジン誘導体等、少数例があるのみである。

【0003】その第1の理由は、直鎖アルキル基を親油基、グアニジン塩基を親水基とする構造の化合物を、例えば繊維用柔軟剤あるいは毛髪用リンス剤として用いた場合、そのカチオン性による繊維あるいは毛髪への吸着性に優れるものの、べたついたり、重い仕上がりとなり、仕上がり性能に難点があることが挙げられる。

【0004】その第2の理由は、一般に、グアニジン誘導体の精製法が複雑であるためである。従来は、反応後、分取液体クロマトグラフィー、カラムクロマトグラフィー、溶媒抽出、再結晶等の精製法を、必要に応じて組合せて用いている。

【0005】アルギニン誘導体あるいはアミド基含有グアニジン誘導体は、特公昭51-22055、特開平2-80667、特開平2-243614、特開平4-34080に記載されているごとく仕上がり性能が良好で、汎用の四級アンモニウム型カチオン界面活性剤と比較してもより優れた性能を有する。しかし、その精製法は未だ複雑で、上記精製法で精製したもので、水および/またはアルコール溶液とした場合、不溶物が生じる場合がある。例えば、これら誘導体を毛髪化粧料として使用した場合、微量の不純物の混在のために安定性に問題が生じる場合がある。

【0006】したがって、高性能のアルギニン誘導体およびアミド基含有グアニジン誘導体のうち、構造によりバリエーションがあり、かつより安価に製造可能と考えられる、水および/またはアルコールへの溶解性に優れたアミド基含有グアニジン誘導体の合理的製造法の開発が望まれていた。

【0007】

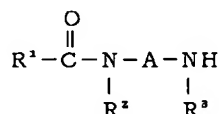
【発明が解決しようとする課題】本発明は、高純度でしかも水および/またはアルコールへの溶解性および安定性に優れたアミド基含有グアニジン誘導体またはその塩を有利に製造する方法を提供することを目的とする。

【0008】

【課題を解決するための手段】本発明によれば、下記一般式（I）（化1）

*【化1】

*

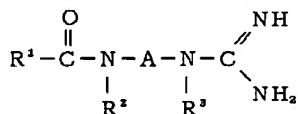


... (I)

（式中、R¹は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R²、R³は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシアルキル基であり、同一でも異なっても良い。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基である。）

※る。）で表わされるアミドアミンを、加温減圧処理あるいは加温窒素バブリング処理をした直後、もしくは二酸化炭素フリーの雰囲気下で保存した後、グアニジン化反応試剤を用いてグアニジン化し、次いで不純物を除去することを特徴とする下記一般式（II）（化2）

【化2】



... (II)

（式中、R¹は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R²、R³は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシアルキル基であり、同一でも異なっても良い。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基である。）で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法が提供され、特に、前記アミドアミンのグアニジン化反応を行なう際に、少量のアルコール類またはエーテル類の存在下に行なうこと、或いは、前記不純物を除去する手段が、晶析であること、そして、該晶析工程において、特に結晶析出および濾過温度が、グアニジン化反応工程で副生するビスアミドの晶析溶媒に対する溶解度が、少なくとも0.1%となる温度以上であることをそれぞれ特徴とする前記アミド基含有グアニジン誘導体またはその塩の製造方法が提供される。

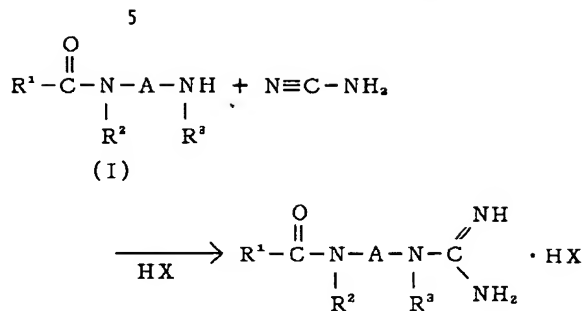
【0009】即ち、本発明者らは、かかる現状において、鋭意研究を重ねた結果、アミドアミンを、加温減圧処理あるいは加温窒素バブリング処理をした直後、もしくは二酸化炭素フリーの雰囲気下（例えば窒素雰囲気下）で保存した後、反応温度を制御しながら通常の方法でグアニジン化し、水および/またはアルコール溶液での不溶物を解明し、晶析等の比較的簡単かつ一段の操作

で、高純度でかつ水および/またはアルコールへの溶解性に優れたアミド基含有グアニジン誘導体を製造可能であることを見出し、本発明を完成した。

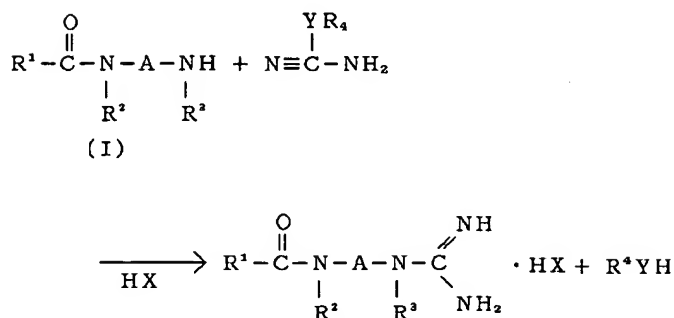
【0010】以下、本発明を更に詳細に説明する。本発明の製造方法における反応は、以下表1の反応式

（I）、（II）等により示される。本発明は、①アミドアミン（例えば、一般および/または二級アミノ基を有するジアミンと、一般のアシル化剤との反応で得られる）を前記本発明の前処理を行ない、次いで②少量のアルコール類またはエーテル類等の溶剤を添加する等の方法で反応温度を制御し、副反応を抑制しながら、一般の無機酸あるいは有機酸存在下で、シアナミド、S-メチルイソチオ尿素等の通常の反応試剤でグアニジン化反応を行い、アミド基含有グアニジン誘導体粗反応物を得、③粗反応物中に含まれる少量の未反応アミドアミン、未反応グアニジン化試剤、副生するジアミンのビスアミドおよび副生尿管誘導体等を一段の精製工程により除去することにより、水および/またはアルコール溶液にした場合、経時で沈殿物を生じることなく、安定性に優れた高純度アミド基含有グアニジン誘導体を得る方法に関するものである。

【表1】



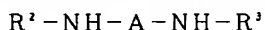
…反応式 (I)



…反応式 (II)

(式中、 R^1 、 R^2 、 R^3 およびAは前記と同じ基である。 R^4 は、炭素数1～4の直鎖または分岐鎖のアルキル基である。HXは、無機酸あるいは有機酸を表わす。Yは、SまたはOである。)

【0011】本発明に用いられアミドアミンは公知の方法*



(式中、 R^2 、 R^3 は、水素原子または炭素数1～4のアルキル基、ヒドロキシアルキル基である。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基である。)ジアミンの具体例としては、ジアミノメタン、エチレンジアミン、N-メチルエチレンジアミン、N、N'-ジメチルエチレンジアミン、N-エチルエチレンジアミン、N、N'-ジエチルエチレンジアミン、N-プロピルエチレンジアミン、N、N'-ジプロピルエチレンジアミン、N-ブチルエチレンジアミン、N、N'-ジブチルエチレンジアミン、N-第三ブチルエチレンジアミン、N、N'-ジ第三ブチルエチレンジアミン、N-メチル-N'エチルエチレンジアミン、1,2-ジアミノプロパン、1-メチルアミノ-2-アミノプロパン、1-アミノ-2-メチルアミノプロパン、1,3-ジアミノプロパン、3-メチルアミノプロピルアミン、1,3-ジ(メチルアミノ)プロピルアミン、3-エチルアミノプロピルアミン、3-プロピルアミノプロピルアミン、3-ブチルアミノプロピルアミン、3-第三ブチルアミノプロピルアミン、3-(2-ヒドロキシエチルアミノ)プロピルアミン、1,2-ジアミノブタン、1,4-ジアミノブタン、1,3-ジア

＊で合成できる。アミドアミンのジアミン部分は、一般および/または二級アミノ基を有するジアミンであり、下記一般式(III)(化3)で表わすことができる。

【化3】

…(III)

ミノ-1-メチルプロパン、1,3-ジアミノ-2-メチルプロパン、1,4-ジアミノ-1-メチルブタン、1,4-ジアミノ-2-メチルブタン、1,6-ジアミノヘキサン、1,8-ジアミノオクタン、1,10-ジアミノデカン等があげられる。これらは単独または2種以上を組合せて使用することができる。

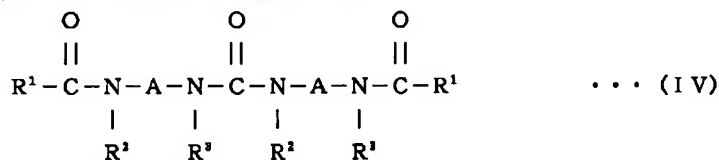
【0012】アミドアミンのアシル部分は、直鎖もしくは分岐鎖の短鎖あるいは長鎖脂肪酸残基であり、酢酸、プロピオン酸、酪酸、イソ酪酸、カプロン酸、オクタン酸、カプリン酸、ラウリン酸、ミリスチン酸、パルミチン酸、ステアリン酸、イソステアリン酸、オレイン酸、エライジン酸、リノール酸、リノレン酸、アラキジン酸、ベヘニン酸、ヤシ油脂肪酸、パーム核油脂肪酸、パーム油脂肪酸、牛脂脂肪酸等があげられる。これらは単独または2種以上を組合せて使用することができる。

【0013】本発明に用いられるグアニジン化反応試剤は、シアナミド、S-メチルイソチオ尿素、S-エチルイソチオ尿素、O-メチルイソチオ尿素、O-エチルイソチオ尿素等が挙げられる。

【0014】本発明方法におけるアミド基含有グアニジンまたはその塩は、前記したように、アミドアミンを前

処理し、次いでグアニジン化反応させ、精製することにより得られる。前処理条件、反応条件及び精製条件は、反応試剤等の物性に左右されるが、ここではモノラウロイルエチレンジアミン（アミドアミンと略称）をシアナミドでグアニジン化する場合を例にとり、以下に反応条件を示す。

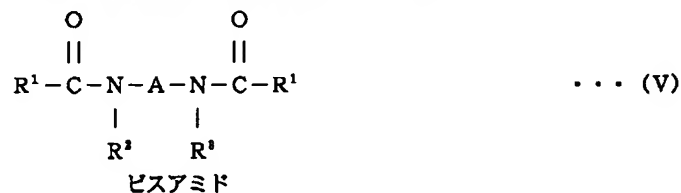
【0015】 ①まず、アミドアミンを加温減圧処理あるいは加温窒素バブリング処理もしくは二酸化炭素フリーの雰囲気下（例えば窒素雰囲気下）で保存する。加温減圧処理あるいは加温窒素バブリング処理をしない場合、も



（式中、 R^1 、 R^2 、 R^3 及びAは、前記と同じ基である。）

【0016】 通常、加温減圧処理、あるいは加温窒素バブリング処理は、内圧10～700hPa（10～500mmHg）程度の減圧下、アミドアミンが熔融する温度約60℃～150℃で、10分～3時間行ない、また、二酸化炭素フリーの雰囲気下での保存は、例えば窒素、ヘリウム、ネオン、アルゴン等不活性ガス雰囲気下で常温において反応仕込み直前まで行なう。

【0017】 次いで②前処理したアミドアミンを塩酸等の無機酸、酢酸等の有機酸などで中和し、シアナミドを粉体のまま、或いは融点以上に加温して、もしくは飽和溶解度量より多いイソプロピルアルコール等のアルコール系溶媒またはテトラヒドロフラン等のエーテル系溶媒に溶解し、一括、または滴下により添加する。シアナミド滴加の場合、滴加時間は特に制限されないが、製造効率の観点から、0.1～3時間の範囲が好ましい。反応温度は60℃～120℃、好ましくは80℃～100℃の範囲である。60℃以下では、反応速度が遅く、120℃以上ではシアナミドの重合反応等好ましくない副反応が起こり、いずれの場合も不適切である。なお、シアナミドを無溶媒で添加すると、発熱反応のため反応温度制御に注意を要するが、アルコール類又はエーテル類の※



【化6】

＊しくは二酸化炭素を含む雰囲気下に保存した場合、アミドアミンが二酸化炭素を吸収し、次に行なうグアニジン化反応の過程で下記一般式（IV）（化4）に示す尿素誘導体を副生し、精製後水および／またはアルコール溶媒とした時に、経時で沈殿を生じる場合があり、加温減圧処理、加温窒素バブリング処理、もしくは二酸化炭素フリーの雰囲気下（例えば窒素雰囲気下）での保存は、必須である。

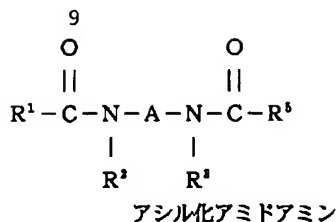
【化4】

※存在下に反応を行なうと反応温度制御が容易であり好ましい。

【0018】 ③こうして得られたアミド基含有グアニジン誘導体粗反応物は、以下に述べる精製方法により精製する。アミド基含有グアニジン誘導体粗反応物は、通常の精製方法で精製すれば、不純物がかなり除去でき、粉体のまま使用する場合に問題ないが、化粧品、医薬品、その他の用途に、水溶液、乳化物等の製剤化のうえ製品化する場合、少量不純物の存在が、製品の保存安定性に大きな影響を与えるため、これらの不純物を微量にまで除去する必要がある。

【0019】 不純物は、未反応原料化合物、及び副生物である。不純物には、未反応アミドアミン、未反応シアナミド、およびジシアンジアミドが含まれることは容易に予測できるが、これら3種の化合物を十分に除去し、事実上含有量0にしたものでも、水および／またはアルコール溶液とした場合に、微量の沈殿が生ずることがある。本発明者らは、この沈殿を集め、分離、分析したところ、下記一般式（V）、（VI）で表わされる化合物が沈殿の原因であることを見出した。これらはいずれも、水および／またはアルコールへの溶解度が低いため、沈殿となって析出する。

【化5】



... (VI)

(Guanidinationの際、酸として、有機酸 $\text{R}^5 - \text{C} - \text{OH}$ を用いた場合生成する。)

)

【0020】以上ビスアミド等の不純物除去は、数々の方法が採用可能であるが、例えば、晶析により精製する場合、以下の条件で行うのが好ましい。アミド基含有グアニジン誘導体粗反応物に、テトラヒドロフラン、メチルエチルケトンの様な、グアニジン誘導体の溶解度が、温度により大きく変化する溶媒を、2~10倍(重量比)添加し、沸点まで加温し、必要により熱時濾過した後、徐々に冷却する。前記一般式(V)、(VI)に示したビスアミド等の、晶析溶媒に対する溶解度は、温度依存性があり、ある温度を境に、急激に溶解度が変化するが、特に一般式(V)、(VI)に示したビスアミドの内溶解度のより低い化合物の溶解度が、少なくとも0.1%となる温度以上の一定温度に保ち、十分目的物を結晶化させた後濾過し、結晶を真空乾燥して溶媒を除去する。加える溶媒量は、2倍未満では結晶化操作中に高粘度となったり、十分不純物を除去できない等の欠点があり、10倍より多い場合は、収率が低く、いずれの場合も好ましくない。また、一般式(V)、(VI)に示したビスアミドの内結晶化温度での溶解度の低い方の化合物の晶析溶媒に対する溶解度が0.1%未満である温度の場合、精製品を水および/またはアルコール溶液とした時に、経時で微量の沈殿を認めることがあり、好ましくない。

【0021】以上の操作により、高純度でかつ水および/またはアルコールへの溶解性、溶液状態での安定性に優れたアミド基含有グアニジンまたはその塩を製造することができる。

【0022】

【実施例】以下実施例をあげて、さらに詳細に説明するが、本発明はこれらに限定されるものではない。なお%は重量基準である。

【0023】実施例1 ラウロイルアミドエチルグアニジン塩酸塩の合成

(1) モノラウロイルエチレンジアミンの前処理

攪拌機、温度計、真空・窒素導入管を備えた500ml四ツ口フラスコに、モノラウロイルエチレンジアミン

(アミドアミンと略、純度:97.2%、未反応ラウリン酸:0.8%、ビスアミド:2.0%)121g

(0.5モル)を仕込み、80℃に保ちながら、減圧窒素導入を3回繰り返し、窒素置換した。

10 【0024】(2) ラウロイルアミドエチルグアニジン塩酸塩の合成

前処理したアミドアミンに、濃塩酸(36%)48.2g(0.475モル)を、系内温度が100℃を超えないように注意しながら滴下、中和した。別に、シアナミド31.5g(0.75モル)をイソプロピルアルコール31.5gに溶解し、アミドアミン95%塩酸塩中に、系内温度を80~90℃に保ちながら一時間かけて滴下した。滴下終了後、同じ温度で3時間熟成を行い、濃塩酸(36%)2.5g(0.025モル)を加え、完全中和した後、溶媒を減圧留去した。収量:170g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率:93.5%、純度:88.1%、未反応アミドアミン:2.6%、副生ジシアンジアミド:7.0%、ビスアミド:1.4%、副生尿素誘導体:traceであった。

【0025】(3) ラウロイルアミドエチルグアニジン塩酸塩の精製

攪拌機、温度計を備えた1l四ツ口フラスコに、(2)で得た粗生成物100gをとり、テトラヒドロフラン300gを加え、80℃に加熱して粗生成物を完全に溶解した。1℃/分の割合で、40分かけて40℃まで冷却し、結晶が析出してから1時間40℃に保温し、十分結晶を析出させた。結晶を濾別して40℃2時間真空乾燥して精製ラウロイルアミドエチルグアニジン塩酸塩を得た。収量:75g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度:99.5%、未反応アミドアミン:0.5%、副生ジシアンジアミド:0.01%以下、ビスアミド:0.01%以下、副生尿素誘導体:検出せず、であった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドの、テトラヒドロフランに対する溶解度は、40℃で0.5%であった。

【0026】実施例2 ラウロイルアミドブチルグアニジン酢酸塩の合成

(1) モノラウロイルブチレンジアミンの前処理

攪拌機、温度計、真空・窒素導入管を備えた500ml四ツ口フラスコに、モノラウロイルブチレンジアミン

(アミドアミンと略、純度:98.4%、未反応ラウリン酸:1.0%、ビスアミド:0.6%)135g

(0.5モル)を仕込み、80℃に保ちながら、減圧窒素導入を3回繰り返し、窒素置換した。

【0027】

(2) ラウロイルアミドブチルグアニジン酢酸塩の合成
前処理したアミドアミンに、酢酸30g(0.5モル)を、系内温度が100℃を越えないように注意しながら滴下、中和した。別に、シアナミド25.2g(0.6モル)をイソプロピルアルコール25.2gに溶解し、アミドアミン酢酸塩中に、系内温度を80~90℃に保ちながら一時間かけて滴下した。滴下終了後、同じ温度で3時間熱成を行った後、溶媒を減圧留去した。収量：189g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.8%、純度：92.4%、未反応アミドアミン：1.9%、副生ジシアンジアミド：2.9%、ビスアミド：0.4%、アセチル化アミドアミン：1.6%、副生尿素誘導体：traceであった。

【0028】

(3) ラウロイルアミドブチルグアニジン酢酸塩の精製
攪拌機、温度計を備えた11四ツ口フラスコに、(2)で得た粗生成物100gをとり、メチルエチルケトン300gを加え、80℃に加熱して粗生成物を完全に溶解した。1℃/分の割合で、30分かけて50℃まで冷却し、結晶が析出してから1時間50℃に保温し、十分結晶を析出させた。結晶を濾別して40℃、2時間真空乾燥して精製ラウロイルアミドブチルグアニジン酢酸塩を得た。収量：80g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：99.5%、未反応アミドアミン：0.4%、副生ジシアンジアミド：0.01%以下、ビスアミド：0.01%以下、アセチル化アミドアミン：0.1%、副生尿素誘導体：検出せずであった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドの、メチルエチルケトンに対する溶解度は、50℃で0.1%であった。

【0029】実施例3

(1) ラウロイルアミドエチルグアニジン酢酸塩の合成
実施例1(1)と同様に前処理したモノラウロイルエチレンジアミンに、酢酸30g(0.5モル)を、系内温度が100℃を越えないように注意しながら滴下、中和した。別に、シアナミド25.2g(0.6モル)を添加溶解し、反応温度を90℃を越えないように時々冷却しながら5時間反応した。収量：176g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.2%、純度：91.1%、未反応アミドアミン：2.7%、副生ジシアンジアミド：3.1%、ビスアミド：1.4%、アセチル化アミドアミン：1.5%、副生尿素誘導体：traceであった。

【0030】

(2) ラウロイルアミドエチルグアニジン酢酸塩の精製
攪拌機、温度計を備えた11四ツ口フラスコに、(1)で得た粗生成物100gをとり、メチルエチルケトン300gを加え、80℃に加熱して粗生成物を完全に溶解した。1℃/分の割合で、30分かけて50℃まで冷却し、結晶が析出してから1時間50℃に保温し、十分結晶を析出させた。結晶を濾別して40℃、2時間真空乾燥して精製ラウロイルアミドエチルグアニジン酢酸塩を得た。収量：79g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：99.6%、未反応アミドアミン：0.4%、副生ジシアンジアミド：0.01%以下、ビスアミド：0.01%以下、アセチル化アミドアミン：0.01%以下、副生尿素誘導体：検出せずであった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドの、メチルエチルケトンに対する溶解度は、50℃で0.2%であった。

【0031】実施例4

(1) ラウロイルアミドブチルグアニジン酢酸塩の合成
実施例2(2) ラウロイルアミドブチルグアニジン酢酸塩の合成において、シアナミド溶解溶媒としてイソプロピルアルコールの代わりにテトラヒドロフランを用いた他は、同様に反応させた。収量：189g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.8%、純度：92.4%、未反応アミドアミン：1.9%、副生ジシアンジアミド：2.9%、ビスアミド：0.4%、アセチル化アミドアミン：1.6%、副生尿素誘導体：traceであった。

【0032】

(2) ラウロイルアミドブチルグアニジン酢酸塩の精製
攪拌機、温度計を備えた11四ツ口フラスコに、(1)で得た粗生成物100gをとり、テトラヒドロフラン300gを加え、80℃に加熱して粗生成物を完全に溶解した。1℃/分の割合で、55分かけて25℃まで冷却し、結晶が析出してから1時間25℃に保温し、十分結晶を析出させた。結晶を濾別して40℃、2時間真空乾燥して精製ラウロイルアミドエチルグアニジン酢酸塩を得た。収量：85g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：99.4%、未反応アミドアミン：0.5%、副生ジシアンジアミド：0.01%以下、ビスアミド：0.01%以下、アセチル化アミドアミン：0.1%、副生尿素誘導体：検出せずであった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドの、テトラヒドロフランに対する溶解度は、25℃で0.1%であった。

【0033】比較例1

50 実施例2(1)モノラウロイルブチレンジアミンの前処

理において、アミドアミンを、大気中に常温で3日間放置した後、減圧窒素置換を行わずに反応、晶析したところ、収量：82g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：98.5%、未反応アミドアミン：0.7%、副生ジシアジアミド：0.01%以下、ビスアミド：0.05%以下、アセチル化アミドアミン：0.4%、副生尿素誘導体：0.3%であった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃2日後に沈殿を生じ *

*た。

【0034】

【発明の効果】本発明の前記製造方法により、得られるアミド基含有グアニジン誘導体およびその塩は、高純度でしかも水および/またはアルコールの溶解性溶液状態での安定性に優れており、しかも本発明の製造方法により、工業的に有利に目的物のアミド基含有グアニジン誘導体またはその塩を製造することができる。

【手続補正書】

【提出日】平成6年5月25日

【手続補正1】

【補正対象書類名】明細書

【補正対象項目名】0010

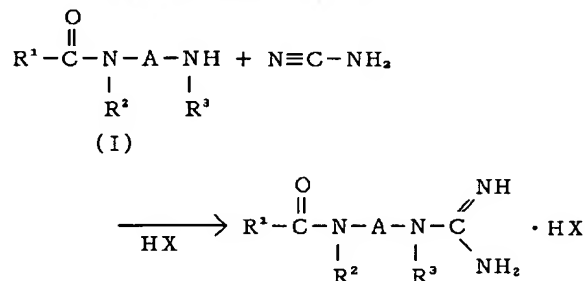
【補正方法】変更

【補正内容】

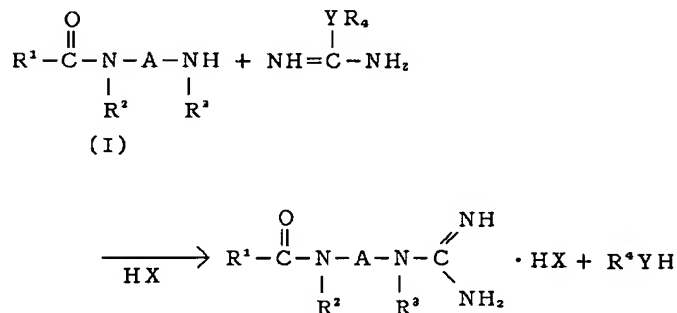
【0010】以下、本発明を更に詳細に説明する。本発明の製造方法における反応は、以下表1の反応式(I)、(II)等により示される。本発明は、①アミドアミン(例えば、一般および/または二級アミノ基を有するジアミンと、一般のアシル化剤との反応で得られる)を前記本発明の前処理を行ない、次いで②少量のアルコール類またはエーテル類等の溶剤を添加する等の方※

※法で反応温度を制御し、副反応を抑制しながら、一般の無機酸あるいは有機酸存在下で、シアナミド、S-メチルイソチオ尿素等の通常の反応試剤でグアニジン化反応を行い、アミド基含有グアニジン誘導体粗反応物を得、③粗反応物中に含まれる少量の未反応アミドアミン、未反応グアニジン化試剤、副生するジアミンのビスアミドおよび副生尿素誘導体等を一段の精製工程により除去することにより、水および/またはアルコール溶液にした場合、経時で沈殿物を生じることなく、安定性に優れた高純度アミド基含有グアニジン誘導体を得る方法に関するものである。

【表1】



…反応式(I)



…反応式(II)

(式中、R¹、R²、R³およびAは前記と同じ基である。R⁴は、炭素数1～4の直鎖または分岐鎖のアルキ

ル基である。HXは、無機酸あるいは有機酸を表わす。Yは、SまたはOである。)

【手続補正2】

【補正対象書類名】明細書

【補正対象項目名】0011

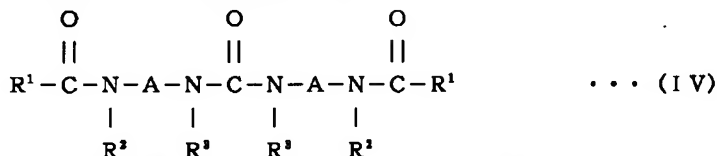
【補正方法】変更

【補正内容】

【0011】本発明に用いられるアミドアミンは公知の*



(式中、 R^2 、 R^3 は、水素原子または炭素数1~4のアルキル基、ヒドロキシアルキル基である。Aは、炭素数1~10の直鎖または分岐鎖のアルキレン基あるいはアルケニレン基である。)ジアミンの具体例としては、ジアミノメタン、エチレンジアミン、N-メチルエチレンジアミン、N、N'-ジメチルエチレンジアミン、N-エチルエチレンジアミン、N、N'-ジエチルエチレンジアミン、N-プロピルエチレンジアミン、N、N'-ジプロピルエチレンジアミン、N-ブチルエチレンジアミン、N、N'-ジブチルエチレンジアミン、N-第三ブチルエチレンジアミン、N、N'-ジ第三ブチルエチレンジアミン、N-メチル-N'エチルエチレンジアミン、1,2-ジアミノプロパン、1-メチルアミノ-2-アミノプロパン、1-アミノ-2-メチルアミノプロパン、1,3-ジアミノプロパン、3-メチルアミノプロピルアミン、1,3-ジ(メチルアミノ)プロピルアミン、3-エチルアミノプロピルアミン、3-プロピルアミノプロピルアミン、3-ブチルアミノプロピルアミン、3-第三ブチルアミノプロピルアミン、3-(2-ヒドロキシエチルアミノ)プロピルアミン、1,2-ジアミノブタン、1,4-ジアミノブタン、1,3-ジアミノ-1-メチルプロパン、1,3-ジアミノ-2-メチルプロパン、1,4-ジアミノ-1-メチルブタン、※



(式中、 R^1 、 R^2 、 R^3 及びAは、前記と同じ基である。)

【手続補正4】

【補正対象書類名】明細書

【補正対象項目名】0016

【補正方法】変更

【補正内容】

【0016】通常、加温減圧処理は、内圧10~700 hPa程度の減圧下、60℃~150℃で、10分~3時間行ない、加温窒素バブリング処理は、窒素を吹き込みながら60℃~150℃で、10分~3時間行ない、また、二酸化炭素フリーの雰囲気下での保存は、例えば窒素、ヘリウム、ネオン、アルゴン等不活性ガス雰囲気下で常温において反応仕込み直前まで行なう。

【手続補正5】

*方法で合成できる。アミドアミンのジアミン部分は、一級および/または二級アミノ基を有するジアミンであり、下記一般式(III)(化3)で表わすことができる。

【化3】



※1,4-ジアミノ-2-メチルブタン、1,6-ジアミノヘキサン、1,8-ジアミノオクタン、1,10-ジアミノデカン等があげられる。これらは単独または2種以上を組合せて使用することができる。

【手続補正3】

【補正対象書類名】明細書

【補正対象項目名】0015

【補正方法】変更

【補正内容】

【0015】先ず、①アミドアミンを加温減圧処理あるいは加温窒素バブリング処理もしくは二酸化炭素フリーの雰囲気下(例えば窒素雰囲気下)で保存する。加温減圧処理あるいは加温窒素バブリング処理をしない場合、もしくは二酸化炭素を含む雰囲気下で保存した場合、アミドアミンが二酸化炭素を吸収し、次に行なうグアニジン化反応の過程で下記一般式(IV)(化4)に示す尿素誘導体を副生し、精製後水および/またはアルコール溶媒とした時に、経時で沈殿を生じる場合があり、加温減圧処理、加温窒素バブリング処理、もしくは二酸化炭素フリーの雰囲気下(例えば窒素雰囲気下)での保存は、必須である。

【化4】

【補正対象書類名】明細書

【補正対象項目名】0020

【補正方法】変更

【補正内容】

【0020】以上ビスアミド等の不純物除去は、数々の方法が採用可能であるが、例えば、晶析により精製する場合、以下の条件で行うのが好ましい。アミド基含有グアニジン誘導体粗反応物に、テトラヒドロフラン、メチルエチルケトンの様な、グアニジン誘導体の溶解度が、温度により大きく変化する溶媒を、2~10倍(重量比)添加し、沸点まで加温し、必要により熱時濾過した後、徐々に冷却する。前記一般式(V)、(VI)に示したビスアミド等の、晶析溶媒に対する溶解度は、温度依存性があり、ある温度を境に、急激に溶解度が変化するが、特に一般式(V)、(VI)に示したビスアミド

の内溶解度のより低い化合物の溶解度が、少なくとも0.1%となる温度以上の一定温度に保ち、十分目的物を結晶化させた後濾過し、結晶を真空乾燥して溶媒を除去する。加える溶媒量は、2倍未満では結晶化操作中に高粘度となったり、十分不純物を除去できない等の欠点があり、10倍より多い場合は、収率が低く、いずれの場合も好ましくない。また、一般式(V)、(VI)に示したビスアミドの内結晶化温度での溶解度の低い方の化合物の晶析溶媒に対する溶解度が0.1%未満である温度の場合、精製品を水および／またはアルコール溶液とした時に、経時で微量の沈殿を認めることがあり、好ましくない。

【手続補正6】

【補正対象書類名】明細書

【補正対象項目名】0029

【補正方法】変更

【補正内容】

【0029】実施例3

(1) ラウロイルアミドエチルグアニジン酢酸塩の合成
実施例1(1)と同様に前処理したモノラウロイルエチレンジアミンに、酢酸30g(0.5モル)を、系内温度が100℃を越えないように注意しながら滴下、中和した。これに、シアナミド25.2g(0.6モル)を添加溶解し、反応温度が90℃を越えないように時々冷却しながら5時間反応した。収量：176g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.2%、純度：91.1%、未反応アミドアミン：2.7%、副生ジシアンジアミド：3.1%、ビスアミド：1.4%、アセチル化アミドアミン：1.5%、副生尿素誘導体：traceであった。

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